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Our Reference	Your Reference	Date
32/64087WO		16 June 2004

Dear Sirs

International (PCT) Patent Application No. PCT/GB2003/001404
Injectable Veterinary Composition for Small Animals
in the name of Norbrook Laboratories Limited

I refer to the written opinion mailed 16 March 2004, and acknowledge the extension of time for submitting a reply as confirmed by the Communication mailed 18 May, 2004. I now submit the Applicant's observations in reply together with proposals for adjusting the claims.

The Examiner has commented on the number of independent claims, and Applicant is prepared to limit the number of independent claims according to the proposed set enclosed herewith. Furthermore, the proposed claims clearly indicate the amounts of Carprofen or Carprofen salt and poloxamer, and the Comparative Examples are not claimed.

The Examiner has referred to three prior art documents and I propose to adopt the same alphanumeric code in discussion of each hereinbelow.

D1 (EP 0955063)

D1 is primarily concerned with an aqueous delivery medium suited for subcutaneous or intramuscular delivery of a pharmaceutically active agent or cosmetic, providing thereby a slow release of said agent, but the D1 inventor of that delivery medium has shown no particular focus on any specific drug, and a long list of pharmaceuticals of differing character is indicated.

Amongst many active pharmaceuticals contemplated for potential use in the proposed "depot" gel-type compositions, there is mentioned the class of analgesics/anti-rheumatics, including Ibuprofen and Tramadol. However, as acknowledged by the Examiner already, Carprofen is not mentioned.

No pharmaceutical formulation examples are given in D1 to demonstrate the effect of the proposed delivery medium, and in the absence of any specific teaching, a person of appropriate skill in this art

would have to conduct research to develop means for directly solubilising Carprofen in water and obtaining a room-temperature stable injectable aqueous formulation thereof. It is recalled here that D1 contemplates use of organic solvents in the first instance to dissolve insoluble ingredients (c.f. [0016] D1).

Since D1 is concerned with a slow-release formulation which in a physiological environment e.g. as in intramuscular injection as described in D1, is a gel-depot type of composition, this reference is remote from the injection solutions described in this application. A formulation of the D1 type cannot be used intravenously due to the likelihood of venous/capillary blockage or embolism. Therefore, D1 is not a suitable starting point for addressing the problems observed in Carprofen formulation, e.g. requiring auxiliaries such as in EP- A-0 280 887, with the resulting problems of side effects.

Thus the invention disclosed by the Applicant is not described nor contemplated in D1 and, we respectfully submit that the amended claims define patentable subject matter over D1.

D2 (CH 663 788)

I can agree that Carprofen is specifically discussed in this German language document, and its use together with an essential amino acid, e.g. L-Lysine or L-Arginine, to produce a salt such as Carprofen-L-lysinate is mentioned. It is also noted that parenteral pharmaceutical compositions using an inert carrier are described. However, it should be remarked that in each of the worked examples Carprofen is introduced as an alcoholic solution (methanol or methylene chloride/methanol) as part of the formulation preparation process. When looking at the actual product, one may consider Example 4d) which does not provide an aqueous solution formulation but does provide a suppository containing Carprofen.lysinate in a non-ionic surfactant based on polyethylene glycol and a poloxamer. With the benefit of hindsight, the Examiner considers that D2 seems to suggest Norbrook's invention is lacking in inventive step. However, this is certainly an incorrect view because, D2 is not a reference relating to delivery solutions of Carprofen or salts, but describing first how to make certain salts, and then use of those salts for making solid unit dose forms. The problem is a different one from that considered by Norbrook and the solution quite different. Therefore, the Norbrook invention is not described therein, nor suggested thereby.

D3 (US 5 283 067)

This reference contemplates a freeze-dried formulation suitable for the preparation of a stable, aqueous suspension for the parenteral administration of an NSAID, particularly one characterised by an acetic acid group (rather than the propionic group characteristic of Carprofen or Ketoprofen). Therefore, the teaching of W3 is entirely on the issue of a particular dry formulation that may be prepared for use as a stable aqueous suspension for parenteral administration. This is generally recognised as involving a mechanism of absorption when the dose is administered by subcutaneous, intracutaneous, and intramuscular injection. This may be contrasted with injection into a fluid of distribution for which the current invention is suitable.

Furthermore, even combining D3 with D2 does not lead directly to the invention made by Norbrook. Firstly the disclosures are not complementary, one relates to solid dosage forms, and the other to dry formulations, the latter intended for later make-up to injectable form. If D3 actually taught stable injection solutions, it would be illogical to prepare the dry formulation. Moreover, the D3 reference relates to injectable suspensions, whereas Norbrook provides an injectable solution.

Therefore, the Examiner is respectfully requested to re-consider the references in the light of the foregoing submissions and the amendments made to the claims.

The following points are also submitted. The stability of the injectable solution of the invention was discussed in comparison with the prior art on page 9 of the original disclosure. However, claim 2 is withdrawn at this time without prejudice. The Examiner has also commented on the Examples used to illustrate the invention, but the Applicant is not obliged to do more than describe the invention and illustrate it with reference to worked examples. Other poloxamers are commercially available and still further poloxamers could be specially prepared. The specification discusses poloxamers, especially values for x, y, z, on page 3, and points to a preferred poloxamer. The following example is also within the scope of the invention as contemplated by the Applicant.

The poloxamer is Lutrol F127 (Poloxamer 407):

Carprofen 5.0% w/v

L-Arginine EP 3.1% w/v

Lutrol F127 (Poloxamer 407) 5% w/v

Benzyl Alcohol 1% w/v

SFS 0.25% w/v

Water for Injection ad 100% w/v

This is illustrative of a formulation using a poloxamer where x = 98, y = 67, and z = 98.

The amended claim 1 is based on the original statements concerning NSAIDs on page 2, and especially with respect to Carprofen or a salt thereof on page 3, lines 16 to 20, and the poloxamer ranges are derived from the same page but particularly taking account of the examples (e.g. Example 3 lower limit). The presence of a preservative is clearly optional as per page 3 line 24, and the Examples given, and having regard to the original claims 1, 3, 10, 11. The Examiner has commented on the presence of "omnibus claims". These claims are permissible in several of the designated states and are retained for the relevant national phases. Such claims are not permissible under e.g. EPC, and will be deleted upon entry to the national phase where appropriate.

Amendment of the description, e.g. to adjust the statements summarising the invention and to acknowledge prior art, is deferred until the relevant national phase.

Since the Applicant has addressed all the points raised in the written opinion, I submit that the file is now in a condition for issue of a favourable IPER having regard to the amended claims now submitted, and the submissions herein on cited art.

Yours faithfully
for Fitzpatricks (Agents for Applicant)

Eric Ede
Authorised Representative
European Patent Attorney

Encs: Amended Claims 1 to 16

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CLAIMS

1. A room-temperature stable injectable solution for veterinary use comprising from 0.5 to 30% (w/v) of Carprofen (6-chloro-α-methyl-carbazole-2-acetic acid) or a physiologically acceptable salt of Carprofen, and from 2.4% to 12% (w/v) of a poloxamer, and water *q.s.* for injection.

2. An injectable aqueous solution according to Claim 1, wherein the Carprofen salt is in the form of an arginine salt.

3. An injectable aqueous solution according to Claim 1, wherein the carprofen salt is in the form of a lysine salt.

4. An injectable aqueous solution according to any one of Claims 1 to 3, wherein Carprofen is present in an amount of from 2.5 to 7.5% (w/v).

5. An injectable aqueous solution according to any one of Claims 1 to 3, wherein Carprofen is present in an amount of from 2.5 to 5% (w/v).

6. An injectable aqueous solution according to any one of Claims 1-5, comprising arginine in an amount of from 1 to 20% (w/v).

7. An injectable aqueous solution according to Claim 1, wherein an organic solvent is present with the poloxamer.

8. An injectable aqueous solution according to Claim 7, wherein the organic solvent is present in the range of 0.5 to 20% (w/v).

9. An injectable aqueous solution according to Claim 1, wherein the poloxamer is $HO(CH_2CH_2O)_x(CCH_3HCH_2O)_y(CH_2CH_2)_zH$ wherein x is 75, y is 30 and z is 75.

10. An injectable aqueous solution for veterinary use according to Claim 1, where the solution is to be employed in treating felines, wherein the lower limit of the range of Carprofen is 0.25% (w/v).

11. An injectable aqueous solution for veterinary use according to Claim 10, comprising arginine in an amount of from 1 to 20% (w/v).

12. A method of producing a room-temperature stable injectable aqueous solution for veterinary use comprising bringing together Carprofen or a physiologically acceptable salt thereof, a poloxamer, and adding sufficient water for injection, to provide a solution containing from 0.5 to 30% (w/v) of Carprofen (6-chloro-α-methyl-carbazole-2-acetic acid) or a physiologically acceptable salt of Carprofen, and from 2.4% to 12% (w/v) of poloxamer.

13. A method according to Claim 12, wherein the poloxamer is $HO(CH_2CH_2O)_x(CCH_3HCH_2O)_y(CH_2CH_2)_zH$ wherein x is 75, y is 30 and z is 75.

14. A method of producing an injectable aqueous solution according to Claim 12 or Claim 13, wherein said method further comprises the inclusion of a preservative.

15. An injectable aqueous solution for veterinary use according to any one of the Examples 1 to 19 hereinbefore.

16. A method of producing an injectable aqueous solution substantially as described in the Example 1.

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